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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,005	ANDERSON, NORMAN L.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,48-51,54-61,64,65,71-78 and 81-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,48-51,54-61,64,65,71-78 and 81-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment August 25, 2008 has been entered. Claims 1-43, 45-47, 52-53, 62-63, 66-70 and 79-80 are cancelled. Claims 81-86 have been newly added. Claims 44, 48-51, 54-61, 64-65, 71-78 and 81-86 are under consideration in this office action.

Withdrawal of Rejections

2. The rejection of claims 44, 47-61, 64-65, 67 and 71-80 under 35 U.S.C. 103(a) as being unpatentable over Geng et al. in view of Nelson et al., has been withdrawn in view of applicants' amendments and arguments.

Response to Arguments

3. Applicant's arguments filed August 25, 2008 have been fully considered but they are not persuasive. Applicant's arguments with respect to claim 44, 47-61, 64-65, 67 and 71-80 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Objection Necessitated By Amendment

Claim Objections

4. Claims 71-72 and 76 are objected to because of the following informalities:

a) Claims 71-72 are dependant upon canceled claim 67. Appropriate correction is required.

b) Claim 76 recites separating the bound peptides from bound peptides. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 60, 73, 76, 78 and 81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Neither the specification nor originally presented claims provides support for: 1) the first and second peptides being selected from among the set of peptides produced by digestion of the target protein to provide high signal to noise in the mass spectrometer; 2) separating the bound peptides from unbound peptides to increases the relative concentration of the bond peptides to unbound peptides by at least 100 fold; 3) subjecting the bound peptides to a concentrating step after elution from said antibodies and before introduction into said mass spectrometer.

Applicant has pointed to page 15, beginning at line 9 of the instant specification for support of claim 60, drawn to the first and second peptides being selected from among the set of peptides produced by digestion of the target protein to provide high signal to noise in the mass spectrometer. However Page 15 states that good monitor peptides is defined by a set of criteria to select peptides that can be chemically

synthesized with high yields, are detected quantitatively, and elicit antibodies when used as antigen. At best, page 15 states that the peptide has a sequence that results from cleavage of the protein with a desired proteolytic enzyme. However, peptides having the a resulting sequence is not equivalent to the first and second peptides being selected from among the set of peptides produced by digestion of the target protein to provide high signal to noise in the mass spectrometer. Therefore, it appears that there is no support in the specification.

Applicants point to page 38, lines 2-3 for support of claims 73 and 76. However, the instant specification teaches “On average, the antibody supports showed a 100-fold enrichment of the 'correct' monitor peptide.” This statement makes no reference to: either separating the bound peptides from unbound peptides, or to increasing the relative concentration of the bond peptides to unbound peptides by at least 100 fold as a result of that separation. Therefore, it appears that there is no support in the specification.

Applicants point to page 30, lines 6-14 for support of claims 78 and 81. However Page 30 drawn to measuring a series of monitor peptides (representing a series of protein analytes), all the corresponding isotopically labeled peptide standards are added to the digest (prepared as above by the computerized fluid handling system). However adding the labeled peptides to the digest does not concentrate the bound peptides. Therefore, it appears that there is no support in the specification for subjecting the bound peptides to a concentrating step after elution from said antibodies and before introduction into said mass spectrometer.

Applicant did not point to support in the specification for 1) the first and second peptides being selected from among the set of peptides produced by digestion of the target protein to provide high signal to noise in the mass spectrometer; 2) separating the bound peptides from unbound peptides to increases the relative concentration of the bond peptides to unbound peptides by at least 100 fold; 3) subjecting the bound peptides to a concentrating step after elution from said antibodies and before introduction into said mass spectrometer. Thus, there appears to be no teaching of the instantly claimed method steps.

Therefore, applicants must specifically point to page and line number support for the identity a method of quantifying an amount of at last a first and second peptide as recited by claims 60, 73, 76, 78 and 81. Therefore, the claims incorporate new matter and are accordingly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 44, 47-61, 64-65, 67 and 71-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geng et al. (J. of Chromatography A, 2000, Vol. 870: page 295-313) in view of Little et al., (US Patent 6,207,2370 published March 27, 2001).

The claims are drawn to a method of quantifying an amount of at least a first peptide and a second peptide in a biological sample, comprising: contacting the sample with (i) a first anti-peptide antibody specific for the first peptide and (ii) a known quantity of a labeled version of said first peptide; contacting the sample with (i) a second anti-peptide antibody specific for the second peptide and (ii) a known quantity of a labeled version of said second peptide; separating peptides bound by the first and second antibodies from unbound peptides; eluting the peptides bound by the first and second antibodies from the antibodies; measuring the amount of the first peptide eluted from the first antibody using a mass spectrometer; measuring the amount of the second peptide eluted from the second antibody using a mass spectrometer; and calculating the amount of the second peptide in the biological sample, wherein the biological sample is a proteolytic digest of a bodily fluid sample.

Geng et al., teach signature peptide approaches to detecting proteins in complex mixtures. Geng et al., teach the sample was digested (page 298). Geng et al., teach classes of peptide fragments were selected by affinity chromatography using different lectin columns (abstract). Geng et al., teach proteins in complex mixtures were digested to create classes of peptide fragments (abstract). Geng et al., teach it is known in the art to purify on an immunoaffinity column and that the ability of immunosorbence to rapidly select the desired analyte for analysis was a great asset (page 296). Geng et al., state that immunosorbents provide higher selectivity than other multidimensional systems (page 296). Geng et al., teach that the enormous complexity of the sample produced by

proteolysis was reduced by using affinity chromatography methods to select specific peptides (page 299).

Geng et al., teach the digested samples were injected onto the column (page 298). Geng et al., teach several purification techniques were disclosed, including serial lectin affinity columns, anion-exchange chromatography, metal affinity chromatography or capillary electrophoresis as being used to separate the fractionated peptides (page 299). The digested human serotransferrin was injected onto affinity column (page 296). Geng et al., teach affinity selection was also performed via affinity columns (page 298). Geng et al., teach the analytes displaced from the column were then eluted (page 298). Geng et al., teach silica based columns, thereby teaching monolithic porous beads as the support (pages 298 and 300). Geng et al., teach sequential loading and elution of the products (page 298). Geng et al., teach a wash of the column, which removed unbound analyte (page 298). Figure 4(b) shows two glycopeptides isolated from the ConA column. Geng et al., teach the eluted peptides were monitored and fractions were collected for MALDI-time of flight mass spectrometry analysis (MALDI-TOF-MS) using the mass spectrometer (page 298). The equations were deduced from the ratios of deuterium-labeled and unlabeled acetylated peptides (page 299). Figure 7 of Geng et al., shows signature peptides having masses at different peaks. Figures 5 and 7 show mass spectrum results from a first and second glycopeptides.

Geng et al., teach at least two differently labeled peptides being prepared and loaded onto the support system and mass spectrometer (page 298). Geng et al., show data teaching proteins being quantified as signature peptides using isotopically labeled

internal standards or first and second peptides. Geng et al., teach this is based on the concept of using and adding the mixture a very similar, but distinguishable substances and determining the concentration of analyte relative to a known concentration of the internal standard (page 308). Geng et al., teach the signature peptides and monitor peptides are all generated by trypsin digestion (page 308). Figure 9(a) depicts the mass spectrum of the labeled and unlabeled peptide. Geng et al., teach isotopes ratios of peptides were determined by MALDI-MS and used to determine the concentration of a peptide relative to that of the labeled internal standard peptides (abstract). Geng et al., teach a method for quantifying the amount of a target protein in a biological sample, such as serum (page 299). Geng et al., state that even with samples having the complexity of human serum, the multidimensional analytical approach of affinity chromatography and mass spectroscopy have sufficient resolution to identify single peptide species (page 312). Finally Geng et al., state that the combined methods provide a powerful method for quantification of multiple proteins in complex mixtures (page 313). However Geng et al do not teach the use of anti-peptide antibodies specific for the first and second peptides.

Little et al., teach diagnostics based on mass spectrometric detection of target polypeptides. Little et al., teach the target polypeptide is isolated prior to being detected by mass spectrometric analysis using a reagent that specifically interacts with the target polypeptide, such as an antibody or metal (col. 3, lines 37-47). Little et al., teach isolating the target polypeptide from a portion of a protein involves proteinases which cut selectively at specific amino acid sequences and in one embodiment, the protein is

obtained and subjected to limited proteolysis prior to mass spectrometric analysis (col. 9, lines 19-25). Little et al., teach further isolating the target polypeptide using an antibody which specifically interacts with an epitope on the target polypeptide and the preparation of specific antibodies is well known in the art (col. 9, lines 26-37). Little et al., teach isolating the target polypeptide by affinity purification using antibodies linked to a solid phase surface wherein the polypeptide can then be eluted from the column and subjected to mass spectrometry (col. 9-10, lines 64-5). Little et al., teach the biological sample can be any material obtained from a living source such as biological fluids like urine, blood, saliva or the like (col. 6, lines 44-50).

It would have been prima facie obvious at the time applicants' invention to modify the method of quantifying an amount of at least a first peptide and a second peptide in a proteolytic digested biological sample by contacting the sample with (i) a first reagent specific for the first peptide and (ii) a known quantity of a labeled version of said first peptide; contacting the sample with (i) a second reagent specific for the second peptide and (ii) a known quantity of a labeled version of said second peptide; separating peptides bound by the first and second reagents from unbound peptides; eluting the peptides bound by the first and second reagents; measuring the amount of the first and second eluted peptides using a mass spectrometer; and calculating the amount of the second peptide in the biological sample, as taught by Geng et al., wherein the modification incorporates antibodies in the affinity chromatography techniques as taught by Little et al., because Little et al., teach the need to target and purify the peptide of

interest with an antibody that specifically interacts with the target polypeptide prior to being detected by mass spectrometric.

One would have a reasonable expectation of success because no more than routine skill would have been required to exchange an antibody into the well known affinity techniques to bind a target because Little et al., teach antibodies are well known in the art to capture and isolate the peptides by affinity purification techniques and allow the eluted peptides to be subjected to mass spectrometry analysis. Moreover, both Geng and Little disclosed alternative reagents and affinity techniques, such as metal chromatography as a means of providing purified peptides. Accordingly, the incorporation of affinity chromatography techniques using antibodies instead of other reagents specific for the peptide, is desirable based on the fact that the enormous complexity of the body fluid sample produced by proteolysis was reduced by using affinity chromatography methods to select specific peptides. Furthermore, one having ordinary skill in the art would have been motivated to incorporate antibodies into the multidimensional method of quantification because such changes are a great asset in mass spectrometric analysis as taught by Geng et al., because purification on immunoaffinity columns and immunosorbence provides rapid higher selectivity of the desired analyte.

Oath/Declaration

7. The declaration of Dr. Steven Carr under 37 CFR 1.132 filed August 25, 2008 is insufficient to overcome the rejection of claims 44, 48-51, 54-61, 64-65, 71-78 and 81-

86 based upon Geng et al. in view of Nelson et al., as set forth in the last Office action because: It refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

For instance, Dr. Carr discusses plasma containing at least one thousand different proteins; however the claims are drawn to a bodily fluid sample. It is noted that the claims embrace more than just plasma samples. Furthermore, it is noted that the instant rejections teach analysis with body fluid and plasma samples. Dr. Carr states that art teaches single protein digest, however the claims do not limit the proteins digested. Dr. Carr states that there was no expectation that antibodies or any other specific binding agent could be used to select peptides from a complex sample digest, however contrary to Dr. Carr's statement; the art teaches selection of peptides using specific binding agents, from a digested complex serum sample.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

8. No claims allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645